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Functional and Mucoadhesive Properties of Native and Modified *Eucalyptus Tereticornis* Gum in Oral Chlorpheniramine Maleate Tablets

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ABSTRACT: As excipients, mucoadhesive polymers increase the resident times of drugs in the mucin/epithelial surface, which is significant for drugs with short half-lives. Native (ETG) and acetylated *Eucalyptus tereticornis* gum (AETG) were incorporated as excipients in directly compressed uncoated and matrix chlorpheniramine maleate tablets, and evaluated for their physicochemical, compressional, release functionalities and mucoadhesive properties. The gums were characterized using photo micrography, rheology, density and compression measurements, swelling capacity (27 ± 0.5^0C and 80 ± 0.5^0C) and FTIR spectroscopy as criteria, and incorporated as excipients (2.5-10.0%w/w) in chlorpheniramine maleate tablets for their compression and release properties, while the mucoadhesive properties of tablet matrix (10-80% w/w gum) were evaluated using pig and cow ilea in 0.1MHCL (pH 1.2). ETG and AETG were spherical to angular in shape. AETG had higher breakdown (907±0.02cP), peak (930±0.01cP) and final (24±1.06cP) viscosities, but lower set back viscosity (3.50±0.03cP), with higher angle of repose, bulk and tapped desities, but lower Carr's index and Hausner's ratio. The ETG had lower deformation characteristics as evidenced by the higher P_k values and lower swelling capacities at both temperatures. FTIR spectra indicated significant presence of more functional groups at 757.13cm^{-1} and 427.66cm^{-1} in AETG due to strong aromatic N-H bond and C-S stretching of aliphatic halogenated compounds. Formulations containing AETG disintegrated and dissolved faster and showed better mucoadhesive profiles in pig ileum. Acetylation of *Eucalyptus tereticornis* gum exhibited better functional properties and generally showed better compressional, release and mucoadhesive properties when compared to the unmodified gum.

KEYWORDS: Chemical modification, Direct compression, Mucoadhesion, *Eucalyptus tereticornis* gum

1. INTRODUCTION

The oral route is the most commonly employed for drug delivery due to convenience, cost-effectiveness, and essentially compliance. The primary site of drug absorption for orally administered medications is usually the small intestine, and the bioavailability of the drug is influenced by the amount of the active drug absorbed across the intestinal epithelium, therefore, it is imperative to ensure that a sufficient, but therapeutically safe quantity of the active paharmaceutical ingredient is made available within this environment (Mathias *et al*, 2010). To overcome the relatively short gastrointestinal time and improve localization for controlled drug delivery systems, bioadhesive polymers that adhere to the mucin/epithelial surface have been investigated (Abruzzo *et al*, 2015; Kalu et al, 2007) The term bioadhesion can be defined as an interfacial phenomenon in which two materials, at least one of which is biological, are held together for an extended period employing interfacial forces. If the adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion, (Rahamatullah, *et al* 2011). Mucoadhesion has several advantages such as increased residence time of the drug, which enhances absorption and drug efficacy, leading eventually to more patient compliance, due to reduction in the dosing frequency (Chopra et al, 2006). Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism, including drugs with short half-lives (Ameye et al, 2005).

The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation (Rahamatullah, 2011). Several polymers have been documented as having good potentials for mucoadhesive drug delivery systems (Ameye et al, 2005;), and the main property of such polymers is the presence of hyroxyl or carboxyl groups which help with the formation of hydrogen bonds with the mucosal surfaces (Grabovac et al, 2005). In recent times, natural gums have been used as excipients in mucoadhesive drug delivery as a result of

availability, good compatibility with biological membranes, reduced toxicity and economic feasibility (Mary-Ann, 2015). Nevertheless, utilization of natural gums is accompanied with host specific problems exemplified by changes in pH stability and dielectric constant at different concentrations, differential solubility/completely dissolution/versus phase separation on storage during the shelf life/storage condition; viscosity changes over a period of time and possibility for microbial contamination (Singla et al, 2000). This necessitated the need to modify these natural gums, with a view to enhancing their functional properties.

Chemical modification is the process of treating natural gums with technically acceptable chemicals with a view to achieving certain desired properties (such as improved flexibility, enhanced thermal and better stability rigidity) in the new modified polymer. The most common approach to chemical modification of polymers for pharmaceutical use include oxidation, hydrolysis, esterification and etherification (Adetunji, 2019). The aim of the present work is to evaluate the mucoadhesive properties of native and etherified *Eucalyptus tereticornis* (Family: *Myrtaceae*) gum (ETG) for potential use in oral drug delivery systems using chlorpheniramine maleate as the model drug.

2. MATERIALS AND METHODS

2.1 Materials

Chlorpheniramine maleate powder BP, talcum powder, dried lactose powder BPC were obtained as gifts from Joyfad Pharmaceutical Laboratories, Akure, Nigeria. Magnesium stearate BP, chloroform water (D/S), glacial acetic acid, ethanol, sodium hydroxide, acetic anhydride, chloro-acetic acid, diethyl ether and distilled water were obtained from the Research Laboratories of the Departments of Pharmaceutics and Industrial Pharmacy, and Pharmaceutical Chemistry University of Ibadan, Ibadan Nigeria. The gum was obtained from the early morning exudates of the trunk of *Eucalyptus tereticornis* (Family: *Myrtaceae*) available as a tree crop in the Botanical Gardens of the University of Ibadan, Ibadan, Oyo State, Nigeria. The tree was authenticated at the Pharmacognosy herbarium, Faculty of Pharmacy, University of Ibadan, Ibadan, Oyo State, Nigeria with herbarium number 1887.

2.2 Collection and purification of *Eucalyptus tereticornis* gum

The brownish gum was collected as early morning exudate from the previously incised trunk of *Eucalyptus tereticornis* tree (Family: *Myrtaceae*) that had been sprayed with ethephon. The exudate was weighed, allowed to dry, and washed thoroughly in chloroform water (D/S) to remove associated earth particles. The washed exudate was spread on a sterile drainer at 35±2^{o}C for 3 hours and transferred to sterile tiles prior to drying in hot air oven at 40^{o}C for 48 hours. The gum was hydrated in chloroform water (D/S) for 5 days, while stirring intermittently, and the resulting mucilage was strained through a clean calico cloth. The gum was precipitated with 95%v/v ethanol, filtered, washed with diethyl ether, and dried at 40^{o}C for 48 hours. The dried gum was pulverized and passed through a number 60 mesh sieve (250µm) (Alur *et al*, 1999*;* Adetunji *et al*, 2013). The percentage of the purified native gum obtained was calculated prior to storing in an air-tight container (Ajakore, 2021).

2.3 Modification of *Eucalyptus tereticornis* gum

The purified *Eucalyptus tereticornis* gum (ETG) was modified by acetylation. Exactly 10g of dry ETG was dispersed in 50 mL of distilled water with constant stirring for 30 minutes. The slurry was adjusted to pH 8.0 with 3% sodium hydroxide prior to adding 1.2 g acetic anhydride before setting down the slurry for five minutes. The pH of the slurry was adjusted to 4.5 with 0.5M hydrochloric acid and filtered through the Whatman No 1 filter paper. The residue obtained was thoroughly washed with distilled water to completely remove the acids that may be present in the product. The resulting product was air dried at 27±2°C to obtain the dried acetylated *Eucalyptus tereticornis* gum (AETG) (Adeyanju, 2015).

2.4 Morphology

The particle sizes and particle size distribution of ETG and AETG were determined using an optical microscope (Olympus model 312545, Japan). Photomicrographs of the gum samples were taken at X 100 magnification to examine the particle shapes. The scanning electron micrography of ETG and AETG was carried out using VEGA3 TESCAN (Germany) electron microscope. Small portion of each sample was placed in aluminum stubs using a double-sided tape and the sample was slightly coated with a layer of carbon in order to aid proper surface and cross-section visualization and also prevent excess charging of the sample. All samples were examined at accelerated voltage.

2.5 Determination of bulk and tapped densities

Fifty grams each of ETG and AETG was separately transferred into a 50 mL measuring cylinder at an angle of 45^{o}. The height at which the powder reached (mL) was recorded and the bulk density was calculated as the ratio of the weight to the volume of the gum (g/mL) in the cylinder. The tapped density for each sample was then determined by applying one hundred taps to the cylinder containing the bulk weight of the gum. The tapped density for each sample was then calculated as the ratio of the weight to the tapped volume of the gum (g/mL). The determinations were made in triplicates (Adetunji et al, 2013).

2.6 Determination of Hausner's ratio

The Hausner's ratio was seperately determined as the ratio of the Tapped Density to the Bulk Density for the ETG and AETG. The determinations were made in triplicates (Herman et al, 1989).

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad (1)$$

2.7 Determination of Carr's index

Carr's Index was calculated from the results obtained from the bulk and tapped densities of the ETG and AETG by using the equation (2). The determinations were made in triplicates (Adetunji *et al*, 2013).

$$\text{Carr Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

2.8 Particle density

The particle densities of the ETG and AETG were separately determined using the pycnometer method with xylene as the displacement fluid. A 50 mL pycnometer bottle was weighed when empty (W_1), filled with completely xylene the difference between the two weights was determined (W_2). A 2 g quantity (W_3) of ETG (or AETG), was transferred into the filled pycnometer bottle and the excess solvent was wiped off after displacement, the bottle was weighed again (W_4). The particle density (Ps) was calculated using the equation below, (Ajakore, 2021).

$$Ps = \frac{W_2W_3}{50[(W_3-W_4) + W_2+W_1]} \quad (3)$$

2.9 Detemination of angle of repose

The angle of repose was determined using an open-ended cylinder of fixed diameter which was placed on a base with similar diameter. Twenty grams (20g) each of the ETG and AETG were separately weighed and allowed to flow freely through the orifice of the funnel at an angle of 45°, to form a heap whose height and diameter were determined. The determination was done in triplicate. The angle of repose was calculated using the equation below, (Adetunji et al, 2013).

$$\tan \Theta = 2h/d \quad (4)$$

Where; h - height of the powder, r - radius of circular heap, d - diameter

2.10 Determination of hydrogen ion concentration (pH)

Two grams (2g) each of the ETG and AETG were separately weighed on an electronic balance and dispersed in 100 mL of distilled water and gently stirred with a glass rod stirrer for 5 mins. The solution was allowed to stand for 10 minutes. The pH was determined using a bench-top pH meter (pH-016, China). This determination was done in triplicate (Emeje et al, 2007).

2.11 Determination of degree of swelling

The swelling index was determined using an established method (Bagirei et al, 2021). The dried ETG (or AETG) (1g) was transferred into 50 mL cylinder, 15 mL of distilled water was added and the slurry was heated in a water bath fitted with a thermostat for about 40 mins., with gentle stirring to prevent the formation of lumps till the temperature rose to 80 ±2 ^{o}C. Centrifuging tubes and cans were weighed to constant weight. The slurry was transferred into the tared centrifuge tubes and weighed. 7.5 mL of distilled water was added, and the resulting solution was centrifuged at 2,200 rpm for 20 mins. The supernatant was decanted immediately after centrifuging into the can. The weight of the sediment was determined. The procedure was also carried out at 27±2^{o}C. The determinations were made in triplicates for each sample and calculated using the formula below:.

$$\text{Swelling} = \frac{\text{Weight of Sediment}}{\text{Initial weight of gum} - \text{Weight of soluble fraction}} \quad (5)$$

2.14 Fourier Transform Infrared (FTIR) Spectroscopy

One milligram of each of the dried ETG (or AETG) was finely grounded to 2µm and thoroughly mixed with 100 mg of dry potassium bromide before placing in a spectrometer cuvette (Perkin Elmer Lt., Chalfont Road, Seer Green, Beaconsfield, Buckinghamshire, UK). The plots of percentage transmittance (%T) versus wave number (cm^{-1}) were made to determine the characteristic functional groups present in the sample (Ajakore, 2021).

2.15 Determination of rheological properties

Rheological characteristics were determined with a Rapid Visco Analyzer (RVA), (model RVA 3+), Network Scientific, Australia). A 0.625g quantity of dried ETG (or AETG) was weighed into a pre-dried empty canister; distilled water (25 mL) was transferred into the canister containing the sample to form 2.5 %w/v slurry, which was heated to 95 ^{o}C prior to cooling to 50 ^{o}C within 2 minute holding time at a rate of 11.25 ^{o}C/min. Peak viscosity, trough, breakdown, final viscosity, set back, peak time, and pasting temperature were determined with the aid of thermocline for windows software connected to the computer (Newport Scientific), The procedure was carried out for samples incorporated at concentrations 2.5 %w/w, 5.0 %w/w, 7.5 %w/w, and 10 %w/w (Ajakore, 2021)

2.16 Determination of loose bulk density of tablet formulation

The determination of the loose bulk density at zero pressure (p_o) of each tablet formulation (containing ETG or AETG as excipients) was carried out by pouring a known weight of the sample at an angle of 45 ^{o}C through a funnel into a measuring cylinder with a diameter of 25 mm and a volume of 50 mL. The determination was carried out in triplicates and the loose bulk density, ρ_o, values were calculated using the following equation, (Adetunji et al, 2013).

$$\rho_o = \frac{W}{\pi r} x \frac{1}{2h} \quad (9)$$

Where w is the weight of the sample in the cylinder, r = radius of the cylinder, h = height of the sample in the cylinder

2.17 Heckel Plots

The Heckel plot of In(1/1-D) against applied pressure (P) was plotted for the different formulations. Values of K and A were obtained from the slope and intercept respectively. The mean yield pressure, Py, was determined as the reciprocal of the slope while the relative density, D_A was obtained from Equation 25. Values for the relative density at low pressures, D_B, were obtained from the difference between, D_A and D_O, (Adetunji *et al*, 2013).

$$A = In[1/(1- D_A)] \quad (10)$$

$$D_B = D_A - D_O \quad (11)$$

2.18 Kawakita Plots

The volume of the formulations at zero pressure (Vo) was determined using equation 12. The volume of the tablets at different compression pressures, Vp was also calculated. The degree of volume of reduction, C, was calculated from equation 27. Kawakita plots of P/C against applied pressure, P, were plotted for the different formulations. Values of 'a' and 'b' were obtained from the slope and intercept respectively (Adetunji et al, 2013).

$$V_o = \pi r^2 h \quad (12)$$

$$C = \frac{[V_o - V]}{V_o (1 - abP)} = abP \quad (13)$$

2.19 Compression of Tablets

Chlorpheniramine maleate tablet formulations containing ETG or AETG or gelatin (in different concentrations) and other ingredients as excipients (Table 1) were weighed and premixed for 15 minutes. The powder blend was compressed into tablets using a Carver hydraulic hand press (model C, Carver Inc, Menomonee Falls, Wisconsin, U.S.A), equipped with a 10.5mm flat-faced punch and die set lubricated with 1% dispersion of magnesium stearate in acetone before compression at 1 metric tonne. (Adetunji *et al*, 2013). Matrix tablets containing 10, 20, 30 and 40.0%w/w chlorpheniramine maleate with corresponding concentration of 90, 80, 70 and 60% ETG or AETG were also directly compressed. *In-vitro* drug release studies from the matrix tablets were conducted for 14 hours at 37±0.2°C in a dissolution medium with a rotating basket providing agitation of 100 rpm. 0.1M HCL was used as the dissolution media, (Adetunji *et al*, 2013).

Table 1: Formulae for directly compressed tablets

Materials	Batches (%w/w)				
	A	**B**	**C**	**D**	**E**
Chlorpheniramine maleate	5.0	5.0	5.0	5.0	5.0
Polymer (native *Eucalyptus tereticornis* gum or modified *Eucalyptus tereticornis* gum)	-	2.5	5.0	7.5	10.0
Talc	2.0	2.0	2.0	2.0	2.0
Spray dried lactose	93.0	90.5	88.0	85.5	83.0

2.20 Crushing strength and percentage friability tests

Crushing strength (CS) tests were carried out in triplicates on ten tablets selected from each of the uncoated regular tablets using a tablet hardness tester (MHT-100, Model P&M 01, Pharma Alliance Group, Indonesia). Tablets that broke into two equal halves were accepted for the crushing strength tests. The DBK Instruments, Mumbai-6, Model 40FTA01, tablet friability apparatus was used in determining the tablet friability (FR) at a speed of 25 rpm for 4 minutes. After the rotation was complete, the tablets were re-weighed from which the percentage loss was calculated. The CSFR of each tablet was also determined from the values of crushing strength and friability (Adetunji et al, 2013).

2.21 Disintegration test

The disintegration time for the uncoated regular tablets was determined in 900 mL of distilled water at a temperature of 37±0.5^{o}C using the DBK disintegration testing apparatus (Type 40TDA01, India). The time taken for each tablet to break up and pass through the mesh screen was recorded. This was done in triplicates and the mean disintegration time was calculated for each batch, (USP, 2011)

2.22 Dissolution test

The *in-vitro* dissolution rate of the tablet was determined in 900 mL of 0.01N HCL using the DBK dissolution test apparatus (Type 40DRT01, Indoia). Each tablet was placed in the sample basket, which was lowered into the dissolution apparatus maintained at a temperature of 37±0.5^{o}C before the rotation was started at 100 rpm. Aliquots of 5 mL were withdrawn from the dissolution medium at pre-determined intervals, and replaced with an equal volume of 0.01N HCl, maintained at the same temperature. The absorbance of each sample was recorded at a wavelength of 265 nm and the total concentration of the drug in each medium was determined (USP, 2011).

2.23 Mucoadhesion test

The mucoadhesion study was carried out to determine the time it would take the matrix tablets (containing different ratios of the drug and gum10.0-90.0%w/w gum) attached to freshly excised intestinal mucosa of pig (or cow) to detach. The rotating cylinder method, which is a slightly modified dissolution apparatus described in the USP was used. A segment of the intestinal mucosa was fixed on a stainless-steel cylinder with the basolateral side facing the cylinder.The tablet was pressed on the apical side and the cylinder was transferred into the medium containing 0.1M HCl buffer, pH 1.2 medium. The rotation speed was set to 50 rpm and the time taken for the tablet to detach from the mucosa was observed and recorded. Similar tests were carried out using the intestinal mucosa of cow (Adetunji et al 2013).

2.24 Statistical analysis

All the results obtained were statistically evaluated using mean (n=3) and standard deviation.

3.0 RESULTS AND DISCUSSION

The abundance of natural polymers has led to recent upsurge in the exploitation of these polymers as excipients in drug delivery systems. Several physical and chemical modifications have also been made to these polymers in attempts to enhance their functional properties in drug formulations. (Kumar *et al*, 2014). In this study, the mucoadhesive functionality of *Eucalyptus tereticornis* (Family: *Myrtaceae*) gum (ETG) was enhanced by acetylation (AETG) and incorporated as excipients in directly compressed chlorpheniramine maleate tablets for evaluation of compression properties. Matrix tablets containing different ratios of ETG or AETG and chlorpheniramine maleate were also prepared to assess the mucoadhesive properties of the polymer.

3.1 Properties of native and modified *Eucalyptus tereticornis* gum

The particle density, bulk density and tapped density of ETG and AETG are presented in Table 2. At various unit operations of tablet production such as filling, mixing, granulation, and compression, the bulk and tapped densities of materials give insight into

the packing behaviour of powders (Adetunji et al, 2013). Bulk density, which is the total mass of powder particles divided by the total volume they occupy, is affected particle shape, particle size and size distribution, and the tendency of the particles to adhere to one another (Odeniyi et al, 2011). High bulk density is important in tablet compression because of a reduction in the volume of the die content. High bulk density values may occur due to the sifting of smaller particles between the larger ones (Babalola *et al*, 2014) and the acetylated gum tends to be more densely packed compared to the native gum. Tapped density represents the maximum packing density of a powder (or blend of powder) achieved under the influence of a defined, externally applied force (Kalu et al, 2007). The ranking of bulk and tapped densities was observed to be AETG > ETG. This implies that the acetylation of the gum led to the formation of denser particles, which will favour better compressibility. Hausner's ratio provides an insight on the degree of densification that could result from vibration of the feed hopper during tableting (Ajakore et al, 2021*)*. The higher the Hausner's ratio, the greater the propensity to form a compact mass (Olayemi et al, 2011). Hausner's ratio higher than 1.25 indicates poor flow. The Hausner's ratio of AETG have values lower than 1.25, which indicates good flow, while the ETG exhibited poor flow due to higher Hausner's ratio values. This same observation was made when the results obtained from the Carr's indices were considered (AETG, 19% < ETG, 66%), implying that the AETG had a better measure of flowability and compressibility than ETG. The qualitative measure of the cohesiveness or the tendency of a material to flow, for instance, from hoppers through the feed frame into the dies of the tableting machine can be assessed using the angle of repose measurements (Ajakore et al, 2021). A uniform flow of powder would help minimize weight variations and ensure uniformity of content in tablets produced. Angle of repose below 30° indicates good flow properties and are considered appropriate for solid dosage formulations (Mary-Ann, 2015), It was observed that the modified and native gum samples both had values greater than 30°, which could be a pointer to poor flow properties. This result seems to contradict other previously mentioned flow property assesors, however, the method used for determining the angle of repose (static method) could be a limiting factor in this study.

3.2 Swelling Properties

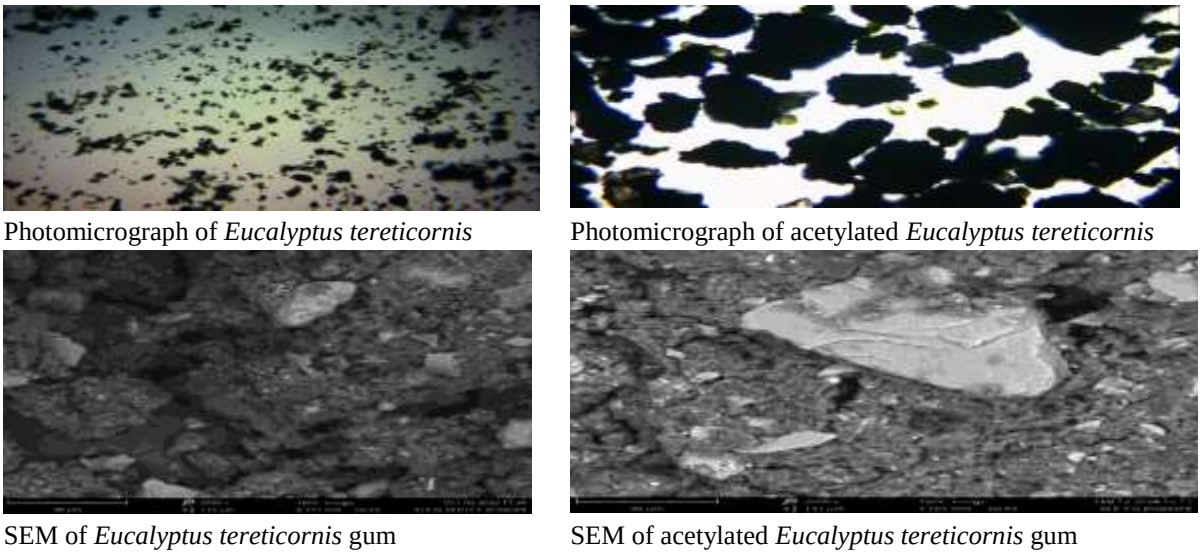
The swelling capacity of the AETG and ETG provide evidence of magnitude of interaction within the lattice structure of the gum and between water molecules. It has also been suggested that the swelling characteristics of a pharmaceutical polymer could be used in the preliminary determinations of the properties of some excipients, especially the ability of such polymer to absorb moisture (Olayemi et al, 2021*)*. The ranking for swelling capacity for the gum samples at 27 °C and 80 °C was AETG > ETG. The weakening of the intrinsic binding forces within the crystal lattice of the modified polymer (AETG) could have been enhanced due to the introduction of more functional groups as a result of the acetylation process, thus leading to rapid swelling observed at both low and high temperatures (Pérez & Bertoft, 2010) The pH values for the gum samples were comparable with the 4.5-7.0 specification of United States Pharmacopoeia for dried gum.

Table 2: Physicochemical properties of Polymers (mean ± SD, n=3)

Parameters	*Eucalyptus tereticornis*	Acetylated *Eucalyptus tereticornis*
Particle Density (g/cm^3)	1.43±0.12	1.03±0.29
Bulk Density (g/cm^3)	0.03±0.06	0.01±0.68
Tapped Density (g/cm^3)	0.01±0.07	0.01±0.33
Carr's Index	66.02±0.01	19.59±0.03
Hauner's ratio	1.67±0.01	1.24±0.05
Angle of repose (°)	44.0±0.1	37.2±0.2
Swelling capacity in water (27^{o}C)	10.00±1.01	54.02±0.07
Swelling capacity in water (80 ^{o}C)	33.00±0.030	74.0±0.040
pH at 27^{0}C	4.50±0.010	4.40±0.040
pH at 80^{o}C	4.40±0.030	4.20±0.020

3.3 Photomicrograph and scanning electron micrography

The photomicrographs of the gum samples show that the shapes of the AETG and ETG are spherical to angular. The chemical modification (acetylation) of the gum did not significantly alter the shape of the gum. Particle shape has been shown to influence particle re-arrangement at the initial stages of the compaction process, (Ajakore et al, 2021*)*. Hang et al (2017) also emphasized the effects of particle shape on particle margination to vascular walls in cardiovascular diseases. The surface of the ETG particles was smooth, while the surface of AETG was rough, with some truncated end exhibiting superficial porosity.



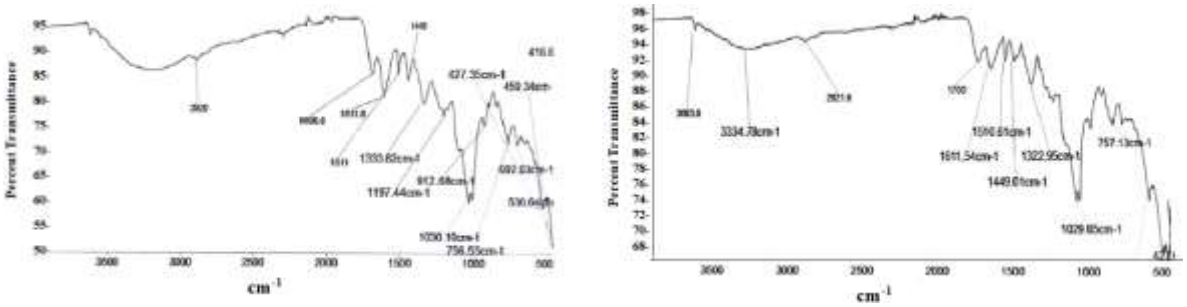
Photomicrograph of *Eucalyptus tereticornis* | Photomicrograph of acetylated *Eucalyptus tereticornis*

SEM of *Eucalyptus tereticornis* gum | SEM of acetylated *Eucalyptus tereticornis* gum

Fig.1: Photomicrographs and Scanning Electron Micrographs (SEM) of native and modified *Eucalyptus tereticornis* gums

3.4 Fourier Transform Infrared Spectroscopy

The FTIR spectra depict the presence of strong and broad absorption bands at 1030.10 cm^{-1} (ETG) and 1029.05 cm^{-1} (AETG) which is an indication of asymmetric C-O stretch to OH bond stretching. The characteristic absorption bands appearing at 756.55 cm^{-1} (ETG) and 757.13 cm^{-1} (AETG) are due to the presence of strong aromatic characters consisting of N-H bond. The fingerprint region consists of C-S stretch and aliphatic halogenated compounds, which are assigned to absorption bands located at 427.35cm^{-1} (ETG) and 427.66cm^{-1} (AETG) (Kumar & Khatkar, 2017) The results revealed the presence of amine, methyl, and hydroxy groups. There is evidence of more functional groups in the FTIR spectra of the AETG, however the fingerprint regions for the spectra of AETG and ETG are almost superimposable, indicating that the acetylation did not significantly affect the crystallinity of the native gum.

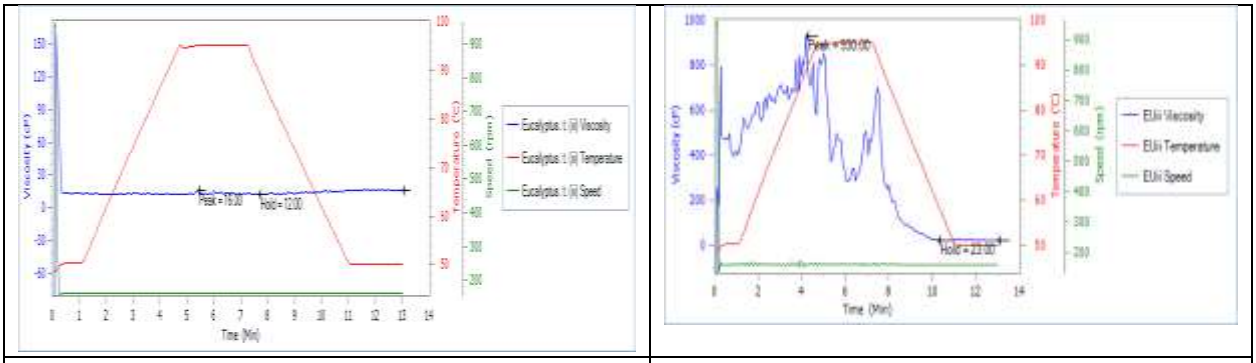


(a) FTIR Plot of *Eucalyptus tereticornis* gum | (b) FTIR Plot of acetylated *Eucalyptus tereticornis* gum

Fig.2: FTIR Plots of native and modified *Eucalyptus tereticornis* gums

3.5 Rheological profile

The peak and breakdown viscosity values of polymers are measures of the stability of the polymer, with high values indicating resistance to breakdown. Lower peak time and temperature of gums have been reported to imply that such gums are sensitive to heat and could form high viscosity gel or paste (Olayemi et al, 2021). The rheological profiles show that AETG has a higher final viscosity and breakdown viscosity than ETG. This may be due to the lower susceptibility of AETG to heat changes during the heating and cooling cycle (breakdown) as a result of the prersence of more functional groups to stabilize the crystals of the acetylated gum. ETG also exhibited a lower retrogradation as shown by lower breakdown viscosity.



(a) *Eucalyptus tereticornis* gum | (b) Acetylated *Eucalyptus tereticornis*

Fig. 3: Viscoamylographs of native and modified polymer

Table 3: Parameters obtained from the viscoamylograph (mean±SD, n=3)

Rheology parameters	*Eucalyptus tereticornis* gum	Acetylated *Eucalyptus tereticornis* gum
Peak viscosity (cP)	16.00±0.02	93.01±0.05
Peak time (min)	5.40 ±0.04	42.01±0.01
Trough viscosity (cP)	12.01±0.13	23.0±0.03
Breakdown (cP)	4.0±0.07	90.7±0.13
Peak temperature (°C)	65.13±0.02	50.31±0.03
Final Viscosity (cP)	16.01±0.28	24.0±0.27
Set back Viscosity (cP)	3.51±0.17	1.01±0.24

3.6 Heckel and Kawakita Plots

The Heckel model relates the reduction in powder volume to the applied pressure. The P_y gives an insight into the plasticity and softness of the materials. A low value of P_y shows low resistance to pressure, good densification and fast onset of plastic deformation. The rank order of P_y is ETG > AETG. This suggests that ETG has a slower onset of plastic deformation than its modified form. D_B is the rearrangement phase at the early stages of compression. The ranking of D_B is ETG > AETG. The high values of D_B in ETG is probably as a result of particle de-segmentation. The total degree of densification occurring in a powder bed (D_A) is higher in ETG than AETG. Three types of powder compression behaviors have been identified based on the Heckel's equation. Most of the plots exhibited relatively linear and near parallel relationships. This implies that the plots are indicative of type-A materials and that both materials principally undergo primary deformation by plastic flow (Gaylord et al, 2022). From the Kawakita plots, a linear relationship was obtained at all compression pressures employed with correlation coefficient of 0.999 for all formulations. The constants **a** and **b** were obtained from the slope and intercept of the plots respectively. The value of **a** is equal to the minimum porosity of the powder bed prior to compression n, while **b** is related to the plasticity of the material (Lin and Cham, 1995). Values of 1-a is an indication of the packed initial relative density of the formulation. The values of P_k and P_I (obtained from the inverse reciprocal of the values of b, and from 1-aXX respectively) represent the required pressure needed to reduce the powder bed by 50% (Lin and Cham, 1995). Low values of P_k indicate materials that are soft and readily deform plastically under pressure. The value of P_k for the formulation decreased with an increase in polymer concentration.The ranking of the P_k values for the polymers was ETG > AETG, implying that formulations containing ETG exhibited the higher amount of total plastic deformation than formulations containing AETG. The lower the value of P_k, the more the total plastic deformation occurring during compression (Odeku and Itiola, 2003). The value of P_I, which is a measure of the packed initial relative density of the polymer with the application of small pressure or tapping (Adetunji & Olopha, 2021), was higher in formulations containing ETG than formulations containing AETG.

Table 4: Parameters derived from Heckel and Kawakita plots

Polymer	**Concentration**	**Heckel plots**				**Kawakita plots**	
		P_y	D_A	D_0	D_B	P_k (MN/m)	P_I
	0.0	714.286	0.813	0.004	0.809	3.845	0.469
Eucalyptus	2.5	1250.00	0.825	0.002	0.823	3.491	0.487
tereticornis gum	5.0	833.33	0.818	0.003	0.816	3.488	0.481
	7.5	2000.00	0.839	0.003	0.836	3.462	0.476
	10.0	769.231	0.815	0.002	0.813	3.437	0.473

Acetylated	2.5	1111.11	0.597	0.006	0.591	3.417	0.406
Eucalyptus	5.0	2000.00	0.609	0.006	0.603	3.397	0.397
tereticornis	7.5	2000.00	0.608	0.006	0.602	3.385	0.393
gum	10.0	1428.57	0.593	0.007	0.587	3.366	0.390

3.8 Crushing strength (CS), Friability (FR) and CSFR ratio

Crushing strength (CS) is a measure of the ability of a tablet to withstand pressure or stress during handling, packaging and transportation. It is the property of a tablet that reveals its resistance to permanent deformation (Adetunji & Olopha, 2021). Consequently, if a tablet is too hard, it may fail to disintegrate in the required time to meet the dissolution specifications; if it is too weak, it may not withstand the rigours of handling or may lead to dosage dumping when administered. Friability (FR) test is designed to evaluate the ability of the tablet to withstand abrasion during packaging, handling and transportation. For compressed tablets, the percentage loss in weight of less than or equal to 1% is usually considered acceptable. The values of the CS, FR and CSFR for the formulations at a relative density of 0.9, which is representative of commercial tablets are shown in Table 2. A linear relationship was observed for the friability and crushing strength. As the concentration of the polymers increased, there was an increase in the values of the crushing strength and a decrease in the percentage friability. However, only formulations containing the AETG at 7.5 %w/w and 10.0 %w/w passed the friability tests. The CSFR ratio also provides a means of assessing the strength of tablets (Mathias & Husseai, 2010)). The higher the CSFR ratio, the stronger tha tablets. An increase was observed for the tablets with an increase in polymer concentration, with tablets containing AETG showing higher values than tablets containing ETG. The implication of this is that the acetylation led to the incorporation of more functional groups that enhanced the bonds within the crytal lattice of the formulations. This could also be responsible for the reduced tendency of the same set of tablets to undergo fracture or abrasion.

Table 5: Crushing strength (CS), Friability (FR) and CSFR ratio for tablets at relative density of 0.9

Polymer Type	Polymer Conc (%w/w)	Crushing Strength (N)	Friability (%)	CSFR
Eucalyptus tereticornis gum	0.0	50.80±0.02	9.80±0.04	5.18
	2.5	68.10±0.07	9.60±0.06	7.09
	5.0	70.20±0.11	5.60±0.13	12.54
	7.5	76.70±0.14	4.40±0.04	17.43
	10.0	82.60±0.06	4.50±0.06	18.36
Acetylated *Eucalyptus tereticornis* gum	2.5	66.50±0.13	6.20±0.12	10.73
	5.0	74.20±0.02	5.40±0.05	13.74
	7.5	75.70±0.05	0.93±0.01	81.40
	10.0	79.30±0.12	0.87±0.17	91.15

3.9 Disintegration and dissolution profiles

The data obtained from the disintegration and dissolution profiles of the chlorpheniramine maletate tablets at relative density of 0.9 are presented in Table 3. Across all formulations, there was a reduction in the disintegration time as the concentration of the polymers increased. Tablets containing AETG were observed to disintegrate faster than tablets containing the unmodified gum (ETG). Luis et al (2010) proposed a high degree of substitution when polymers are modified by acetylation. This could be responsible for the easy break up that was observed in formulations containing acetylated *Eucalyptus tereticornis* gum. The rate of dissolution of tablets is critical to this process and is influenced by some factors including the tablet hardness and porosity (Odeniyi et al, 2011). Representative plots of the dissolution profiles are shown in Figure 1. The results obtained from the dissolution profile shows that chlorpheniramine maleate tablets containing acetylated *Eucalyptus tereticornis* gum exhibited faster dissolution rates, with an inverse relationship observed between dissolution rate and polymer concentration; consequently formulations containing 2.5 %w/w AETG released 80% of the active ingredient in less than 10 minutes. while formulations containing the 10.0%w/w of the native polymer showed the longest time to release of 80% of the active ingredients in less than 19 minutes.

Table 6: Disintegration and dissolution characteristics of chlorpheniramine maleate tablets at relative density 0.90 (mean ± SD, n=3)

Polymer Type	Polymer Conc (%w/w)	Disintegration Time (min)	t_{50} (mins)	t_{80} (mins)
Eucalyptus tereticornis gum	0.0	0.44±0.01	1.13±0.11	3.26±0.13
	2.5	2.47±0.03	11.24±0.13	14.24±0.04
	5.0	4.36±0.13	12.48±0.19	14.46±0.17
	7.5	8.32±0.15	14.27±0.07	16.26±0.25
	10.0	11.18±0.05	16.12±0.17	18.04±0.13
Acetylated *Eucalyptus tereticornis* gum	2.5	1.33±1.12	6.12±0.12	9.43±0.11
	5.0	2.48±0.06	7.58±0.22	9.55±0.07
	7.5	5.28±0.17	8.37±0.18	11.28±0.04
	10.0	9.44±0.08	9.35±0.14	14.23±0.13

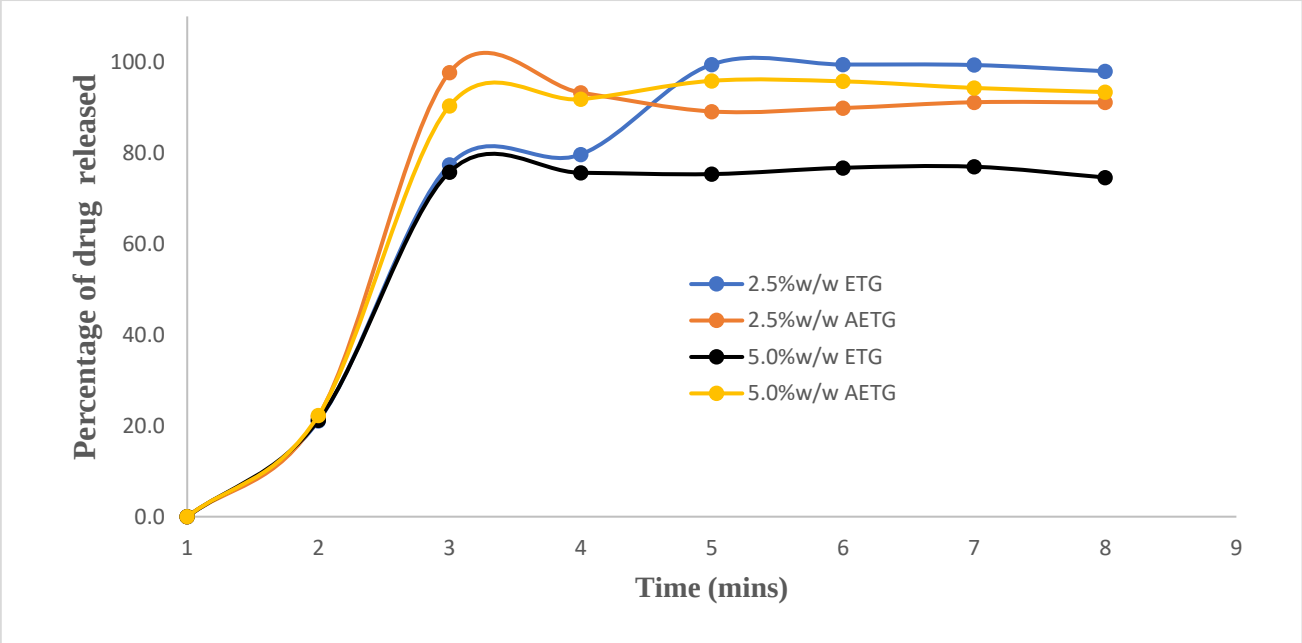


Fig.4: Representative Dissolution plots

3.10 Mucoadhesion properties

The mucoadhesion properties of the chlorpheniramine maleate matrix tablets were determined using both pig and cow ilea to understand the ability of the native and modified gum samples to encourage prolonged residence time in the GI tract when administered. Generally, there was a direct correlation between concentration of polymers and mucoadhesive time for the formulations. Matrix tablets containing acetylated *Eucalyptus tereticornis* gum exhibited better mucoadhesive properties, which was observed in pig ileum compared to cow ileum. The better mucoadhesive properties exhibited in the colon of the pig could be a pointer to the potential use of the formulation in humans, due to the similarities in the morphology of the intestine of humans and pigs (Kararli, 1995)

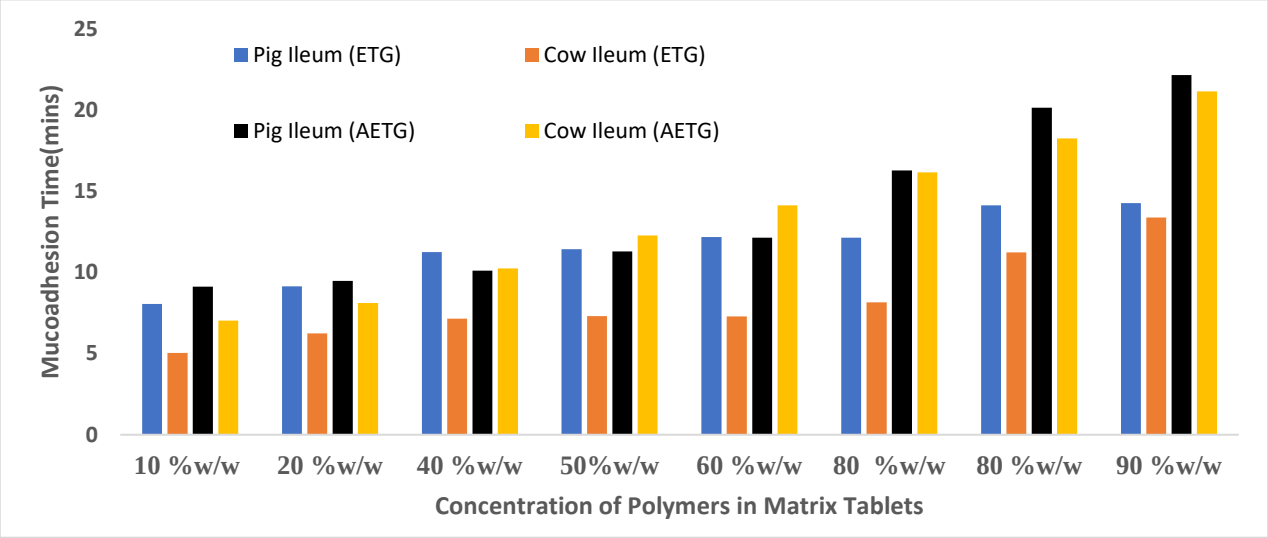


Fig. 5: Plot of mucoadhesion time (mins) against concentration (%w/w)for matrix tablets in 0.1M HCL

CONCLUSION

Acetylated *Eucalyptus tereticornis* gum exhibited better functional properties and generally showed better compressional, release and mucoadhesive properties when compared to the unmodified gum. Studies to validate the enhanced mucoadhesive properties of the acetylated gum at low concentrations (0.5 – 2.0%w/w) and in phosphate buffer (pH 6.8) are on-going.

CONFLICT OF INTEREST: The authors declare no conflict of interest in this study.

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